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A Mitochondrial Etiology of Common Diseases

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Life is the interaction between structure (anatomy), energy (vital force), and information (for structure and energy). The predominant source of energy is mitochondrial oxidative phosphorylation (OXPHOS), the genes of which are dispersed across the chromosomes and the multicopy, maternally inherited, mitochondrial DNA (mtDNA), the mtDNA coding for critical OXPHOS and mitochondrial protein synthesis genes. Deleterious mutations in mtDNA genes, such as the *tRNA*$^{Leu(UUR)}$ m.3243A>G gene, can occur at different percentages of mutant (heteroplasmic). Differences in 3243G heteroplasmy cause different phenotypes from diabetes and autism, to severe neuro-muscular disease, to lethal childhood disease. The different heteroplasmy levels alter mitochondrial metabolism and the altered metabolites are substrates for the chromatin modification enzymes. This changes the epigenome and expression of the nuclear DNA (nDNA) coded mitochondrial genes creating the different phenotypes. Environmental challenges can also alter mitochondrial gene expression. SARS-CoV-2 infection suppresses the transcription of clusters of nDNA genes required for specific subassembly modules of the OXPHOS complexes, thus blocking OXPHOS. SARS-CoV-2 also induces miR2392 and 362 nDNA mRNAs harbor miR2392 binding sites. miR2392 also binds to the mtDNA blocking its transcription. This concerted inhibition of mitochondrial function increases mitochondrial reactive oxygen species (mROS) which activates HIF1α and glycolysis, redirecting substrates toward viral biogenesis. Mitochondrial inhibition in the lung is reversible as viral load declines, but this is not the case for the heart, and continued reduction of heart mitochondrial transcripts correlates with fatality. Acute SARS-CoV-2 airway infection of hamsters causes changes in mitochondrial gene expression in the brain before visceral effects. Hence, SARS-CoV-2 may activate diffusible factors that cause neurological symptoms. Therefore, mitochondrial bioenergetics has broad implications for both inherited and acquired diseases.